



International Journal of Pharmaceutical Research and Development (IJPRD)

Platform for Pharmaceutical Researches & Ideas

www.ijprd.com

TASTE MASKING OF SITAGLIPTIN PHOSPHATE MONOHYDRATE BY ION EXCHANGE RESIN AND FORMULATION OF RAPIDLY-DISINTEGRATING TABLETS

A.Pavankumar^{*1},

Mrs.P.Sumathy, Dr.K.L.Senthilkumar, Dr.R.P.Ezhilmuthu.

¹Padmavathi College Of Pharmacy & Research Institute, Periyanahalli, Dharmapuri- 635205, Tamilnadu.

ABSTRACT

The purpose of this research was to mask the intensely unpleasant taste of Sitagliptin Phosphate Monohydrate and to formulate a rapidly disintegrating tablet (RDT) of the taste-masked drug. Taste masking was done by complexing Sitagliptin Phosphate Monohydrate with Indion 414 in different ratios by the precipitation method. Drug-Resin complexes (DRCs) were tested for drug content, in vitro taste in simulated salivary fluid (SSF) of pH 6.2, and molecular property. Complex that did not release drug in SSF was considered taste-masked and selected for formulation RDTs. The complex with drug-Resin ratio of 1:1 & 1:2 did not show drug release in SSF; therefore, it was selected. The properties of tablets such as tensile strength, wetting time, water absorption ratio, in vitro disintegration time, and disintegration in the oral cavity were investigated to elucidate the wetting and disintegration characteristics of tablets. Crospovidone 8%wt/wt gave the minimum disintegration time. Tablets of batch F2 containing microcrystalline cellulose as Diluent Crospovidone showed faster disintegration, within 25 seconds. Good correlation between in vitro disintegration behavior and in the oral cavity was recognized. Whereas Sitagliptin Phosphate Monohydrate was rated intensely better with a score of 12 for 10 minutes. Tablets of batch F2 also revealed rapid drug release (t_{90} , 7 minutes) in SGF. Thus, results conclusively demonstrated successful masking of taste and rapid disintegration of the formulated tablets in the oral cavity.

Key words: Taste masking, rapid-disintegrating tablets, Sitagliptin Phosphate Monohydrate, Indion 414, superdisintegrants.

Correspondence to Author

A.Pavankumar

Padmavathi College Of Pharmacy & Research Institute, Periyanahalli, Dharmapuri- 635205, Tamilnadu.

Email: arisa.pavankumar@gmail.com

INTRODUCTION

In recent decades, a variety of pharmaceutical research has been conducted to develop new dosage forms. Considering quality of life, most of these efforts have been focused on ease of medication¹. Among the dosage forms developed to facilitate ease of medication, the rapid disintegrating tablet (RDT) is one of the most widely employed commercial Products²⁻⁴. The RDT has remarkable disintegration properties; it can rapidly disintegrate without water in the mouth within a few seconds. When an RDT is placed in the oral cavity, saliva quickly penetrates into the pores causing rapid disintegration.

RDTs are useful in patients^{4,5}, such as pediatric, geriatric, bedridden, or developmentally disabled, who may face difficulty in swallowing conventional tablets or capsules and liquid orals or syrup⁶, leading to ineffective therapy, with persistent nausea, sudden episodes of allergic attacks, or coughing for those who have an active life style. RDTs are also applicable when local action in the mouth is desirable such as local anesthetic for toothaches, oral ulcers, cold sores, or teething⁹, and to deliver sustained release multiparticulate system to those who cannot swallow intact sustained action tablets/capsules¹⁰.

Sitagliptin Phosphate Monohydrate¹⁹ (7-[(3R)-3-amino-1-oxo-4-(2,4,5trifluorophenyl)butyl]-5,6,7,8-tetrahydro-3-(trifluoro-3-(trifluoromethyl)-1,2,4-triazolo[4,3-a] pyrazine phosphate mono hydrate) is an anti diabetic agent shown to be effective in adjuvant treatment for type 2 diabetes. It is a selective dipeptidyl peptidase IV (DPP4) inhibitor which works by enhancing the incretin system in the body, thus decreasing blood glucose. When the body senses hyperglycemia, incretins stimulate the pancreas to release insulin and signal the liver to stop glucose production. The DPP4 enzyme rapidly hydrolyzes the incretin hormones to inactive products. Therefore, inhibiting the enzyme increases the active levels of incretin hormones in the body, including glucagon like peptide1 (GLP1) and glucose dependent insulinotropic peptide (GIP). Sitagliptin Phosphate Monohydrate is an intensely Unpleasant drug; Available online on www.ijprd.com

hence, if it is incorporated directly into an RDT the main objective behind formulation of such a dosage form will definitely get futile^{2,13,14}. Thus in the present study an attempt has been made to mask the taste of Sitagliptin Phosphate Monohydrate and to formulate RDTs with good mouth feel so as to prepare a “patient-friendly dosage form”.

MATERIALS AND METHODS

Materials

Sitagliptin Phosphate Monohydrate was a gift from MSN Laboratories (HYD, India). Indion 414 resin from Ion exchange Ltd; Mumbai, Microcrystalline cellulose (Ceolus KG 802, Asahi Kasei Chemicals Corporation, Tokyo, Japan). The superdisintegrants were crospovidone (Polypasdone XL-10, ISP Technologies, Inc, Calvert City, KY), croscarmellose sodium (Ac-Di-Sol, FMC Biopolymer, Wallingstown, Ireland) and sodium starch glycolate (Primojel, DMV International, Belle Mead, NJ). All other chemicals used in the study were of analytical grade.

Preparation of Drug-Resin Complex (DRC)

Drug was mixed separately with the resins in a drug:resin ratio of 1:1 and 1:2. 25 ml of distilled water was added to the mixtures and stirred continuously on magnetic stirrer, for 7 hrs until the equilibrium was attained. Aliquots from the reaction mixture were withdrawn and filtered through Whatman filter paper no. 41 after every hr and were analyzed after appropriate dilution at 267 nm by UV/VIS spectrophotometer. The process was continued till the concentration values of two consecutive aliquots were almost constant. The readings were taken in triplicate. The resultant complex was filtered through Whatman filter paper no. 41, washed with water to remove the unreacted drug and oven dried at 50°C for 1 hr and stored in air tight glass vial till the further use. Unbound drug in filtrate was estimated spectrophotometrically at 267 nm against blank and drug-loading efficiency was calculated²⁸.

Characterization of DRC Drug Content, In Vitro Taste Evaluation, and Molecular Properties

Drug content was determined by dissolving 200 mg of DRC in 500 ml of simulated gastric fluid (SGF) and analyzing 1ml of appropriately diluted sample at 267 nm. In vitro taste was evaluated by determining drug release in simulated salivary fluid (SSF) (pH 6.2) to predict release in the human

saliva. DRC, equivalent to 100 mg of Sitagliptin Phosphate Monohydrate was placed in 10 ml of SSF and shaken for 7 minutes. The amount of drug released was analyzed at 267 nm.

Table 1. Drug Content and In Vitro Taste Evaluation of DRCS in SSF

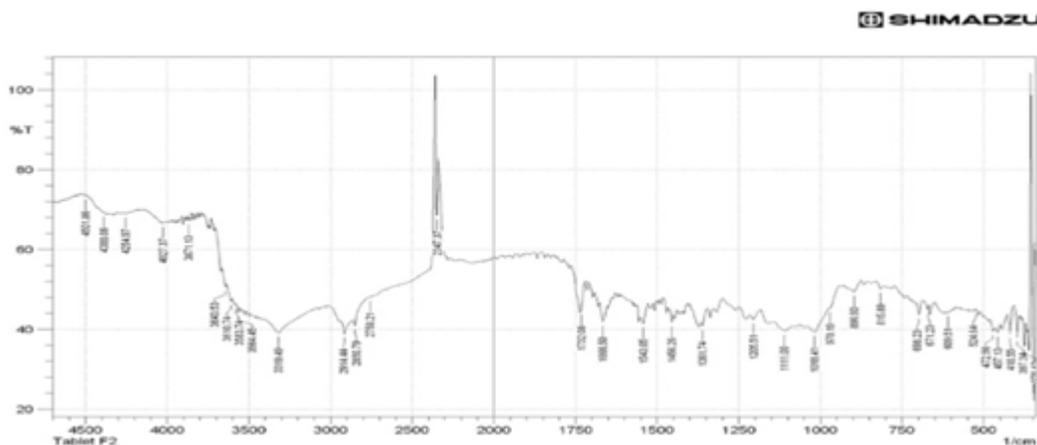
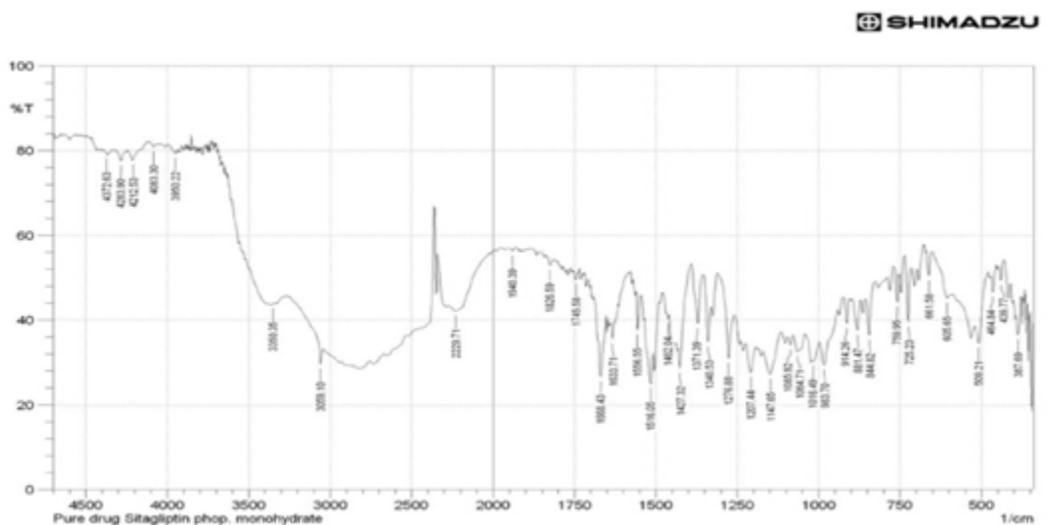
Serial No.	Drug-Resin Ratio	Amount of Sitagliptin per 200mg of DRS	% of Drug Dissolve in SSF
1	1:1	98.18	0.12
2	1:2	97.78	ND

*Results are the mean of 3 observations ± SD.

ND indicates not detectable

Molecular properties on complexation were studied by Fourier transform infrared spectroscopy (FTIR).

Figure 1 & 2. Fourier transform infrared spectra of Sitagliptin Phosphate Monohydrate, and drug-Resin complexed (DRC) Tablet formulation.



Selection of Superdisintegrant and Formulation of RDTs

Before formulation of tablets, the best superdisintegrant among Polyplasdone XL-10, Ac-Di-Sol, and Primojel was screened out. Tablets were prepared in various batches containing a blend of microcrystalline cellulose and as a diluent and superdisintegrant in various concentrations (Table 2). The best superdisintegrant screened was used for the final formulation of tablets (Table 3). Tablets were prepared by direct compression using 10.2mm flatfaced punches.

Physical Properties of the Tablet Blend¹⁵

Physical properties such as bulk density, tapped density, compressibility index, and the angle of repose of blend were determined (Table 4). Bulk density was determined by the USP method I; tapped density was determined by USP method II using a tapped density tester (Electrolab, ETD 1020, Mumbai, India). Percent compressibility and Hausner ratio were calculated using Equations 1 and 2:

$$\text{Percent compressibility} = \{(Dt - Db)/Dt\} \times 100$$

$$\text{Hausner ratio} = Dt/Db$$

Where, Dt and Db are tapped and bulk densities.

Evaluation of Tablets

Wetting Time and Water Absorption Ratio¹⁶

A piece of tissue paper folded twice was kept in a culture dish (internal diameter 5.5 cm) containing ~6 mL of purified water. A tablet having a small amount of amaranth powder on the upper surface was placed on the tissue paper. The time required to develop a red color on the upper

surface of the tablet was recorded as the wetting time. The same procedure without amaranth was followed for determining the water absorption ratio. The wetted tablet was weighed and the water absorption ratio, R, was determined according to the following equation,

$$R = \frac{Wa - Wb}{Wb} \times 100$$

where, Wb and Wa were the weights of the tablet before and after study.

Tablets were also evaluated for hardness, tensile strength, friability, weight variation, and drug content (Table 5).

In Vitro Disintegration Study

In vitro disintegration time for RDTs was determined using USP and modified disintegration apparatus with SSF (pH 6.2) as the disintegrating medium. During this study we made an attempt to develop a more suitable apparatus for RDT (Figure 3) because many reports¹⁷⁻²⁰ indicated the unsuitability of the conventional disintegration test apparatus for RDT. Briefly, the apparatus consisted of a glass beaker of 1000ml capacity with the wire basket positioned in the beaker with the help of a support in a way that when the beaker contained 900 mL of disintegrating medium, the basket had only 6 ml of it. A magnetic bead was placed at the bottom of the beaker maintained at $37 \pm 2^{\circ}\text{C}$. Disintegration time was determined at 25 and 50 rpm and compared with results obtained from the USP disintegration test apparatus and the in vivo disintegration test.

Table 2. Disintegration Time of Different Superdisintegrants

Batch	Disintegrant	Disintegrant %wt/wt	Disintegration Time (Sec)
F1	CRP	4	29
F2	CRP	8	25
F3	CCS	4	34
F4	CCS	8	26
F5	SSG	4	37
F6	SSG	8	30
P1	CRP	4	34
P2	CRP	8	28

P3	CCS	4	36
P4	CCS	8	30
P5	SSG	4	39
P6	SSG	8	30

CRP indicates Polyplasdone XL-10 (Crospovidone); CCS, Ac-Di-Sol (Croscarmellose sodium); SSG, Primojel (Sodium starch glycolate).

Table 3. Composition of Rapid-Disintegrating Tablets

Ingredients, mg	Batch					
	F1	F2	F3	F4	F5	F6
Sitagliptin phosphate mono hydrate – Indion 414 complex	200	200	200	200	200	200
MCC	168	152	168	152	168	152
CP	16	32	-	-	-	-
CCS	-	-	16	32	-	-
SSG	-	-	-	-	16	32
Magnesium stearate	4	4	4	4	4	4
Talc	4	4	4	4	4	4
Aerosil	4	4	4	4	4	4
Aspartame	4	4	4	4	4	4

DRC indicates drug resin complex. Formula for one tablet is shown in the table. Each tablet contains 100 mg of Sitagliptin Phosphate Monohydrate; QS, quantity sufficient.

In Vivo Disintegration Time, Sensory Evaluation of Roughness 20 and Taste Evaluation^{21,22}

In vivo disintegration was performed on 6 healthy human volunteers, from whom informed consent was first obtained. One tablet was held in the mouth after rinsing and the time required for complete disintegration of the tablet was recorded (Table 6). The disintegrated material was held in the mouth for another 60 seconds, and then spat out. The mouth was rinsed with water without swallowing the disintegrated material and, finally, the roughness levels were recorded on a numerical scale ranging from 0 to 3 where 0, 1, 2, and 3 indicate no, slight, moderate, and high roughness, respectively. Taste evaluation was done using the time intensity method on 11 healthy human volunteers from whom informed consent was first obtained. The DRC equivalent of 100 mg of Sitagliptin Phosphate was held in the mouth for 25

seconds and then spat out, and 1 RDT (containing 100 mg Sitagliptin Phosphate) was held in the mouth until complete disintegration. Bitterness was recorded immediately and at several intervals for 15 minutes according to the Unpleasantness intensity scale from 0 to 3 where 0, 0.5, 1, 2, and 3 indicate no, threshold, slight, moderate, and metallic taste. Dissolution Study of Tablets In vitro dissolution study on prepared tablets (batch F2) was done in 500 ml SGF without enzymes using USP type II (paddle) apparatus at 50 rpm and $37 \pm 0.5^{\circ}\text{C}$.

RESULTS AND DISCUSSION

Characterization of DRCs

Percentage drug loading in DRCs was found from for 1:1 and 1:2 is 99.48 and 95.64. No drug release was observed in SSF from complexes with the drug-Resin ratio of 1:1 and ratios with lesser drug, therefore, the ratio 1:2 was considered the optimal DRC with complete masking of Metallic taste for further studies.

Table 4. Angle of repose, Bulk, Tapped density, % compressibility, Hausner ratio.

Property	F1	F2	F3	F4	F5	F6
Angle of repose, degrees	28.91 ± 0.15	20.99 ± 0.26	21.98 ± 1.01	22.55 ± 0.44	20.47 ± 0.25	23.79 ± 0.17
Bulk density, g/cm ³	0.44 ± 0.02	0.51 ± 0.02	0.52 ± 0.02	0.46 ± 0.02	0.54 ± 0.03	0.55 ± 0.02
Tapped density, g/cm ³	0.54 ± 0.03	0.58 ± 0.03	0.60 ± 0.03	0.51 ± 0.03	0.61 ± 0.02	0.67 ± 0.02
% Compressibility	18.14 ± 0.25	12.17 ± 0.17	13.68 ± 1.18	10.37 ± 0.49	12.68 ± 1.42	17.23 ± 0.10
Hausner Ratio	1.205 ± 0.015	1.146 ± 0.005	1.153 ± 0.013	1.119 ± 0.006	1.141 ± 0.016	1.218 ± 0.008

FTIR studies

In the present dissertation work on formulation and *in-vitro* evaluation of rapidly disintegrating tablets of Sitagliptin Phosphate Monohydrate the pure drug and its various formulation P1 –P6 and F1 – F6 are characterized by taking the IR spectra of the drug and some of the representative formulations. IR is one such technique used for the characterization of the formulations.

The IR spectrum of F2 (Drug – Indion 414 (1:1)) formulation exhibited its characteristic absorption bands in the following absorption regions.

Table 5. FTIR Interpretation Ranges

Functional group	Interpretation Range
N-H Stretching	3600- 3200
C-H Stretching	2960- 2850
C=O Stretching	1600- 1450
C=C Stretching	1600- 1475
C-N Stretching	1400- 1040

Since the formulation contains several ingredients in addition to pure drug and polymer there will be a slight difference in the appearance of the spectrum in comparison with spectrum of the pure drug. However the major peaks of the drug in the formulation can be easily distinguished and characterized.

The comparison of the IR spectra of the drug and its formulation F2 suggests that the positions of the characteristic absorption bands for important functional groups and bands are not changed in the respective IR spectrum of both.

As there is no change in the position of the bands in the IR spectra of the two it may be considered that the drug shows same bands in its normal state and its formulation. These observations clearly indicate that the drug has not

interacted with the resin and other excipients used in formulation F2. Hence it can be concluded that there is no interaction of the drug with ingredients of the formulation F2.

Selection of the Superdisintegrant

Initially tablets containing superdisintegrants in the concentrations 4 and 8% wt/wt were tested for disintegration time. Tablets containing Polyplasdone XL-10 showed quick disintegration followed by Ac-Di-Sol and Primojel. The probable reason for delayed disintegration of the tablets with Ac-Di-Sol and Primojel might be due to their tendency to gel more than Polyplasdone XL-10. This result coincides with the findings of Patel et al., 14 wherein they formulated orodispersible tablets of rofecoxib. Hence, Polyplasdone XL-10 was selected for the formulation of RDTs. After selection, the concentration of Polyplasdone XL-10 was further reduced to get the minimum optimal concentration. Polyplasdone XL-8% wt/wt was selected as the optimum concentration that showed minimal disintegration time of 25 seconds. It was observed that further increase in concentration led to the increase in disintegration time. Such delay in disintegration may be because of the higher water requirement by a larger amount of Polyplasdone XL-10, which consequently transformed into swelling force for rapid disintegration of the tablet.

Physical Properties of the Tablet Blend

The tablet blend of all the batches showed good flowability (angle of repose G30-) and compressibility, except batch F1 with an angle of repose of 28.9⁰. Poor flowability of F1 may be attributed to the presence of only microcrystalline cellulose having filamentous particles as a diluent.

Table 6. Comparison of Disintegration Time of Rapid-Disintegrating Tablets and Marketed Tablet by Different Methods*

Formulations	USP Apparatus	Modified Release (50rpm)	Modified Release (25rpm)	In vivo Disintegration
F1	29	31	32	34
F2	25	27	29	28
F3	34	36	35	34
F4	26	29	28	30
F5	37	38	39	38
F6	30	32	31	34

Results are the mean of 3 observations.

Wetting, Disintegration Time, Taste, and Sensory Evaluation of RDTs

Properties like hardness, friability, weight variation, and content uniformity of tablets of all the batches were found to be within acceptable limits.

Tablets of batch F2 containing microcrystalline cellulose in the ratio 1:1 and 8% wt/wt Polyplasdone XL-10 showed faster

disintegration, within 25 seconds. As polyols are readily soluble in water, there exists a competition between Microcrystalline cellulose and Polyplasdone XL-10 for water penetrating into the tablet, consequently leading to poor swelling of Polyplasdone XL-10 with subsequent delay in disintegration.

Table 7. Comparative Taste Evaluation*

Form of Sitagliptin Phosphate Monohydrate	10s	1min	2min	5min	10min	15min
Pure Drug	0.5	3	3	3	2	2
DRC	0	0	0.5	0.5	0	0
Unflavored tablet of DRC	0	0	0	0	0	0
Flavored tablet of DRC	0+	0+	0+	0+	0+	0+

*Results are the mean of 11 observations.

+ indicates palatability; DRC, drug-resin complex.

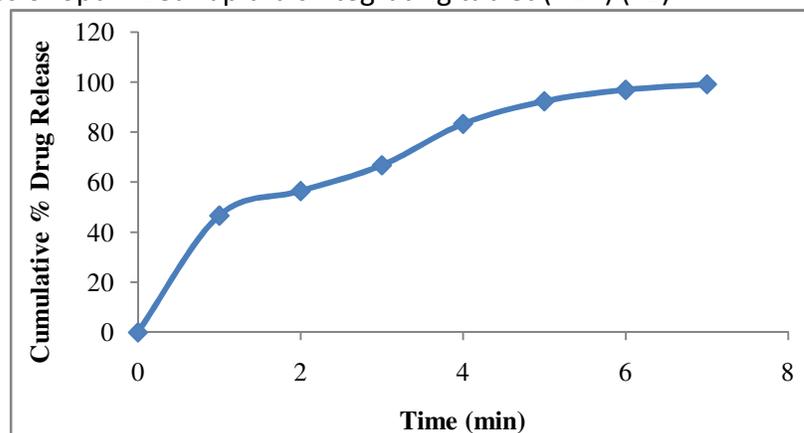
Between the 2 stirrer speeds, 25 rpm was found to provide more comparable results with the in vivo test. Disintegration times of tablets from all the batches at 25 rpm were found nearly same as in vivo disintegration time (Table 6). Thus, the test apparatus with a stirring speed of 25 rpm was considered the most suitable.

The time intensity study for taste in human volunteers of both the DRC and RDT revealed considerable masking of the unpleasant taste of Sitagliptin Phosphate Monohydrate with degree of unpleasant taste below the threshold value (0.5) ultimately reaching to 0 within 15 minutes. Sensory

evaluation of the optimized tablet proved good palatability.

Drug Release from RDT

From the results of the tests, tablets of batch F2 were considered to possess the best physical properties accompanied with quick disintegration and, therefore, tested. The dissolution study of the optimized tablet revealed rapid release of drug (t_{90} of approximately 7 minutes) in SGF, which had at 90 of approximately 240 seconds. The dissolution process might have involved both ion exchange and solubilization of Indion 414.

Figure 3. Dissolution profiles of optimized rapid-disintegrating tablet (RDT) (F2).

CONCLUSION

The study conclusively demonstrated complete taste masking of Sitagliptin Phosphate Monohydrate and rapid disintegration and dissolution of RDT. Taste masking and rapid disintegration of tablets formulated in this investigation may possibly help in administration of Sitagliptin Phosphate in a more palatable form without water during emesis. Thus, the “patient-friendly dosage form” of unpleasant taste drugs, especially for pediatric, geriatric, bedridden, and noncooperative patients, can be successfully formulated using this technology.

REFERENCES

- Hanawa T, Watanabe A, Tsuchiya T, Ikoma R, Hidaka M, Sugihara M. New oral dosage form for elderly patients: preparation and characterization of silk fibroin gel. *Chem Pharm Bull (Tokyo)*. 1995;43:284Y288.
- Ishikawa T, Watanabe Y, Utoguchi N, Matsumoto M. Preparation and evaluation of tablets rapidly disintegrating in saliva containing bitter taste masked granules by compression method. *Chem Pharm Bull (Tokyo)*. 1999;47:1451Y1454.
- Koizumi K, Watanabe Y, Morita K, Utoguchi N, Matsumoto M. New method for preparing high porosity rapidly saliva soluble compressed tablets using mannitol with camphor, a subliming material. *Int J Pharm*. 1997;152:127Y131.
- Kaushik D, Dureja H, Saini TR. Mouth dissolving tablets: A review. *Indian Drugs-Bombay*. 2004;41:187Y193.
- Chue P, Welch R, Binder C. Acceptability and disintegration rates of orally disintegrating risperidone tablets in patients with schizophrenia or schizoaffective disorders. *Can J Psychiatry*. 2004;49:701Y703.
- Shu T, Suzuki H, Hironaka K, Ito K. Studies of rapidly disintegrating tablets in oral cavity using coground mixture of mannitol with crospovidone. *Chem Pharm Bull (Tokyo)*. 2002;50:193Y198.
- Seager H. Drug delivery products and the zydys fast dissolving dosage form. *J Pharm Pharmacol*. 1998;50:375Y378.
- Gohel M, Patel M, Amin A, Agrawal R, Dave R, Bariya N. Formulation design and optimization of mouth dissolve tablets of nimesulide using vacuum drying technique. *AAPS PharmSciTech*. 2004;5:E36.
- Chang RK, Guo X, Burnside BA, Couch RA. Fast dissolving tablets. *Pharm Technol*. 2000;24:52Y58.
- Shimizu T, Sugaya M, Nakano Y, et al. Formulation study for lansoprazol fast disintegrating tablet, III. Design of rapidly disintegrating tablets. *Chem Pharm Bull (Tokyo)*. 2003;51:1121Y1127.
- Health Products and Food Branch. “SUMMARY BASIS OF DECISION (SBD)” PrJANUVIA™ Sitagliptin phosphate monohydrate, 100 mg, tablet Merck Frosst Canada Ltd. Submission Control No. 103039.

12. *Baptist Gallwitz*. "Review of sitagliptin phosphate: a novel treatment for type 2 diabetes"; Vaccume Health & Risk Management 2007; 3(2) 203-210.
13. Reddy LH, Gosh BR. Fast dissolving drug delivery system: A Review of the literature. *Indian J Pharm Sci*. 2002;64:331Y336.
14. Patel DM, Patel NM, Shah RR, Jogani PL, Balapatel AI. Studies in formulation of orodispersible tablets of rofecoxib. *Indian J Pharm Sci*. 2004;66:621Y625.
15. United States Pharmacopeia 24/NF 19. The Official Compendia of Standards. Asian ed. Rockville, MD: United States Pharmacopoeial Convention Inc; 2000:1913Y1914.
16. Kuchekar BS, Badhan AC, Mahajan HS. Mouth dissolving tablets of salbutamol sulphate: a novel drug delivery system. *Indian Drugs*. 2004;41:592Y598.
17. Morita Y, Tsushima Y, Termoz R, Ajioka J, Takayama K. Evaluation of disintegration time of rapidly disintegrating tablets via a novel method utilizing a CCD camera. *Chem Pharm Bull (Tokyo)*. 2002;50:1181Y1186.
18. Watanabe Y, Yamamoti Y, Fujii M, Kondoh M, Shibata Y. A novel method for predicting disintegration time in the mouth of rapid disintegrating tablet by compaction analysis using Tab All. *Chem Pharm Bull (Tokyo)*. 2004;52:1394Y1395.
19. Narazaki R, Harada T, Takami N, Koto Y, Ohwaki T. A new method for disintegration studies of rapid disintegrating tablets. *Chem Pharm Bull (Tokyo)*. 2004;52:704Y707.
20. Watanabe Y, Ishikawa T, Mukai B, et al. Preparation of RDT using new type of microcrystalline cellulose (PH M series) and low substituted hydroxy propyl cellulose or spherical sugar granules by direct compression method. *Chem Pharm Bull (Tokyo)*. 2001;49: 134Y139.
21. Uchida T, Nakamura T, Tanigake A, et al. The effect of various substances on the suppression of the bitterness of quinine–human gustatory sensation, binding, and taste sensor studies. *Chem Pharm Bull (Tokyo)*. 2002;50:1589Y1593.
22. Borodkin N, Sundberg DP. Polycarboxylic acid ion exchange resin adsorbates for taste coverage in chewable tablets. *J Pharm Sci*. 1971;60:1523Y1527.
23. Fernandes CM, Veiga FJ. Effect of hydrophobic nature of triacetyl β -cyclodextrin on the complexation with nifedipine hydrochloride: physicochemical and dissolution properties of the kneaded and spraydried complexes. *Chem Pharm Bull (Tokyo)*. 2002;50:1597Y1602.
24. Schiermeier S, Schmidt PC. Fast dispersible ibuprofen tablets. *Eur J Pharm Sci*. 2002;15:295Y305.
25. *Dennis J. Cada, PharmD, FASHP, FASCP (Editor)*. "Sitagliptin Phosphate"; formulary drug review, *Hospital Pharmacy Vol 42, No 2*, pp 133-140 2007.
26. *Inderbir singh, Rohit kalra*. "Ion Exchange Resins: Drug Delivery and Therapeutic Applications"; *FABAD J. Pharm. Sci* 32, 91-100, 2007.
27. *Siew-Pheng Chan, MBBS (Malaya), FRCP (Edinburgh)* "Sitagliptin Phosphate: The First Available Oral DPP-4 Inhibitor for Type 2 Diabetes" *Medical progress* January 2008: 29-33.
28. *Patel HA, Patel JK, Patel KN, Patel BS*. "Studies on formulation and *in vitro* evaluation of fast dissolving tablets of domperidone". *Int J Ph Sci* 2010; 2(1): 470-76.
29. *Dali SHUKLA, Subhashis CHAKRABORTY*. "Mouth Dissolving Tablets II: An Overview of Evaluation Techniques"; *Sci.Pharm*:77:327-341.
30. *Swamy PV, Areefulla SH, Shirsand SB, Gandra S, Prashanth B*. "Orodispersible tablets of meloxicam using disintegrant blends for improved efficacy". *Indian J Pharm Sci* 2007; 69(6): 836-40.
31. *Shishu, Bhatti A and Singh T*. "Preparation of tablets rapidly disintegrating in saliva containing bitter taste-masked granules by compression method". *Indian J. Pharmaceut Sci* 2007; 80-84.
32. *Shalini sharma and shaila lewis*. "Taste masking technologies: a review"; *IJPPS Vol-2, Issue-2*, 2010, 6-13.

33. *Balamuralidhara V, Sreenivas SA, Gangadharappa HV, Pramodkumar TM.* "Investigation on the effect of different disintegrants on the orodispersible tablets of rabeprazole". *Asian J Sci Res* 2009; 1-8.
34. *Puttewar TY, Kshirsagar MD, Chandewar AV, Chikhale RV.* "Formulation and evaluation of orodispersible tablet of taste masked doxylamine succinate using ion exchange resin". *J. King Saud University* 2010; 1-12.
35. *Rajnibala, Sharma S, Sharma N, Gupta GD.* "Development of non-bitter zolpidem tartrate mouth dissolving tablet". *J. Pharm Res* 2009; 2(9): 1530-1535.
